

A Feasibility Trial of a Brief Positive Affect Intervention to Improve the Effectiveness of Influenza Vaccine Response in Older Adults.

**Final Version 1.1
21st August 2017**

Short title: Mood and Influenza Vaccine Response: A Feasibility Trial

Trial Registration: www.clinicaltrials.gov Identifier: NCT03144518

IRAS Project ID: 226429

Trial Sponsor: University of Nottingham

Sponsor reference: 17039

Funding Source: National Institute for Health Research School for Primary Care Research (NIHR SPCR).

TRIAL / STUDY PERSONNEL AND CONTACT DETAILS

Sponsor:

Contact name

University of Nottingham
Ms Angela Shone
Head of Research Governance
Research and Graduate Services
King's Meadow Campus
Lenton Lane
Nottingham
NG7 2NR
Email: sponsor@nottingham.ac.uk

Chief investigator:

Mr Kieran Ayling
Research Fellow
Division of Primary Care
Tower Building
University of Nottingham
Nottingham
NG7 2RD
Email: kieran.ayling@nottingham.ac.uk
Phone: 01158466908

Co-investigators:

Professor Kavita Vedhara
Professor of Health Psychology
University of Nottingham
Division of Primary Care
Tower Building
University Park
Nottingham, NG7 2RD
Phone: 0115 846 6931
Email: kavita.vedhara@nottingham.ac.uk

Dr Heather Buchanan
Senior Lecturer in Health Psychology
Division of Rehabilitation & Aging,
University of Nottingham
Nottingham
NG7 2UH
Email: heather.buchanan@nottingham.ac.uk

Dr Lucy Fairclough
Lecturer in Immunology
School of Life Sciences,
University of Nottingham,
Nottingham
NG7 2UH
Email: lucy.fairclough@nottingham.ac.uk

Associate Professor Paddy Tighe
Associate Professor in Immunology
School of Life Sciences,
University of Nottingham,
Nottingham
NG7 2UH
Email: paddy.tighe@nottingham.ac.uk

Professor Ian Todd
Professor in Immunology
School of Life Sciences,
University of Nottingham,
Nottingham,
NG7 2UH
Email: ian.todd@nottingham.ac.uk

Dr Simon Royal
General Practitioner
Cripps Health Centre,
University of Nottingham,
Nottingham
NG7 2QW
Email: simon.royal@nhs.net

Dr Mark Wetherell
Reader in Psychobiology & Health Psychology
Department of Psychology,
Northumbria University,
Northumbria
NE1 8ST
Email: mark.wetherell@northumbria.ac.uk

Dr Graziela Figueredo
Advanced Data Analysis Centre,
School of Computer Science,
University of Nottingham
Nottingham
NG8 1BB
Email: grazziela.figueredo@nottingham.ac.uk

Trial / Study Statistician:

Dr Graziela Figueredo
Advanced Data Analysis Centre,
School of Computer Science,
University of Nottingham
Nottingham
NG8 1BB
Phone: 01159514923
Email: grazziela.figueredo@nottingham.ac.uk

Trial / Study Coordinating Centre: Division of Primary Care
School of Medicine
Queen's Medical Centre
Nottingham
NG7 2UH

SYNOPSIS

Title	A Feasibility Trial of a Brief Positive Affect Intervention to Improve the Effectiveness of Influenza Vaccine Response in Older Adults.
Short title	Mood and Influenza Vaccine Response: A Feasibility Trial
Chief Investigator	Mr Kieran Ayling
Objectives	To assess the impact of a brief positive affect intervention on mood, immune function, and antibody response to influenza vaccination in older adults. This feasibility trial will also allow data collection on exploring recruitment, attrition, intervention engagement, and practicality of collecting clinical data available through electronic records to inform the design of a future definitive trial.
Trial Configuration	2 arm parallel randomised controlled trial, with post-trial qualitative interviews/focus groups
Setting	Primary Care
Sample size estimate	<p>As a feasibility study, the sample size has been selected to inform the design of a future definitive RCT allowing us to examine recruitment uptake levels, attrition, intervention engagement, and suitability of data collection methods. It is not our aim to be powered to detect effects in vaccine specific outcomes (e.g., antibody responses, rates of flu like illness) but to provide initial effect size estimates for a future larger RCT.</p> <p>However, our sample size will be sufficient to provide adequate power to detect pre-post differences in positive affect between conditions. A sample of 45 participants would be needed per arm to provide 95% power to detect pre-post differences. We will, therefore, aim to recruit 55 participants per condition to allow for reasonable attrition.</p>
Number of participants	<p>Approximately 110 older adults (65-85 years old). The reason for having an upper limit of 85 years is that after this time immune function can vary much more greatly across individuals – including those over 85 could potentially obscure/alter results and their generalisability.</p> <p>For Staff Interviews – Approximately 8 health care professionals (including GP's, practice manager, health care assistants, nurses etc.) who worked in the recruiting practices.</p>
Eligibility criteria	<p>For Feasibility Trial:</p> <p>Inclusion criteria</p> <p>Males and Females aged 65-85 years (inclusive) Received influenza vaccination for the 2016/17 season Eligible to receive 2017/18 influenza vaccination as part of usual care Ability to give informed consent</p>

	<p>Exclusion criteria</p> <p>Males and Females aged less than 65 or over 85 years (exclusive) Did not receive influenza vaccination for the 2016/17 season Ineligible to receive 2017/18 influenza vaccination as part of usual care Unable to provide informed consent Deemed by health care provider to be: Too physically frail to participate Diagnosed with dementia or other cognitive condition which would make participation difficult Insufficient command of English language Influenza vaccination contraindicated Sufficiently impaired of hearing or vision that exposure to the intervention or control video content as intended would be compromised Those for whom the collection of blood samples is contraindicated.</p> <p>For Post-Trial Staff Interviews:</p> <p>Inclusion criteria</p> <p>Member of staff at a GP practice site involved in the feasibility trial Aware of and observed aspects of the feasibility trial at their site</p> <p>Exclusion criteria</p> <p>Not staff at a GP practice site involved in the feasibility trial Unaware of or did not observe any aspect of the feasibility trial at their site</p>
Description of interventions	<p>Trial will focus on a brief mood intervention (video based approx.15-20 mins length) delivered prior to receipt of the trivalent influenza vaccination (delivered as part of usual care). Pre- and post-intervention mood questionnaires will be collected. Saliva samples will be collected immediately pre- and post-intervention. Blood samples to be taken at 3 times points (baseline, approximately 4 weeks post-vaccination and 16 weeks post-vaccination) to assess vaccine response.</p> <p>Experimental Intervention: Video package designed to induce an increase in positive mood in older adults. Includes comedy clips, uplifting music and positive imagery.</p> <p>Active Control: Video package matched in length and type to experimental intervention but not designed to influence mood.</p>
Duration of study	<p>The trial will be start alongside the 2017/2018 influenza vaccination schedule (i.e., August/September 2017). Participants will be involved for approximately 4 and a half months, which includes all follow-ups. Participants will be asked to give consent for medical records to be examined at 6 months post-vaccination. The main parts of the trial will end when the final participant completes their 16 week post-vaccination follow-up (approx. March 2018), although post-trial focus groups/interviews will occur and medical records will be examined up to 6 months post-vaccination (approx. May 2018).</p>

Randomisation and blinding	1:1 Randomisation, computer generated. Participants blind to nature of other conditions. Researchers and outcome assessors blind to participant allocation until end of trial.
Outcome measures	Psychological outcomes will be measured using questionnaire self-report measures. Vaccine and immune response will be measured using a variety of immunological parameters derived from blood and saliva samples. Feasibility measures (e.g., recruitment uptake, attrition) will be recorded by the chief investigator. Post-trial focus groups/interviews will be qualitatively analysed for themes using thematic analysis.
Statistical methods	While many outcomes of interest will be descriptive in nature (e.g., attrition, recruitment rates), between arm comparisons will be made on several primary and secondary outcomes (positive affect, antibody response, secretory IgA concentration – which is a broad non-specific marker of immunological function, health service utilization) using appropriate statistical tests (e.g., between group t-tests). Intention-to-treat analyses will be favoured where appropriate. Qualitative post-trial interviews/focus groups will be analysed using thematic analysis.

ABBREVIATIONS

AE	Adverse Event
CI	Chief Investigator overall
CRF	Case Report Form
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
ICF	Informed Consent Form
IgG	Immunoglobulin Serotype G
NHS	National Health Service
PI	Principal Investigator at a local centre
PIS	Participant Information Sheet
REC	Research Ethics Committee
R&D	Research and Development department
SAE	Serious Adverse Event

TABLE OF CONTENTS

SYNOPSIS.....	5
Inclusion criteria	5
Exclusion criteria	6
Inclusion criteria	6
ABBREVIATIONS.....	8
TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE.....	11
TRIAL / STUDY OBJECTIVES AND PURPOSE	12
PURPOSE	12
PRIMARY OBJECTIVE	12
SECONDARY OBJECTIVES	12
TRIAL / STUDY DESIGN	12
TRIAL / STUDY CONFIGURATION	12
Primary endpoint	13
Secondary endpoint	13
Safety endpoints	13
Stopping rules and discontinuation	13
RANDOMIZATION AND BLINDING	13
Maintenance of randomisation codes and procedures for breaking code	14
TRIAL/STUDY MANAGEMENT	14
DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT	14
End of the Trial	14
SELECTION AND WITHDRAWAL OF PARTICIPANTS	14
Recruitment	14
Eligibility criteria	15
Inclusion criteria	15
Exclusion criteria	15
Inclusion criteria	15
Expected duration of participant participation	16
Removal of participants from therapy or assessments/Participant Withdrawal	16
Informed consent	16
TRIAL / STUDY TREATMENT AND REGIMEN.....	16
Compliance	18
Criteria for terminating trial	18
TRANSPORT AND STORAGE OF THE TISSUES	18
LABORATORY ANALYSES	19
STATISTICS.....	19
Methods	19
Sample size and justification	19
Assessment of efficacy	20
Assessment of safety	20
Procedures for missing, unused and spurious data	20
Definition of populations analysed	20

ADVERSE EVENTS.....	20
ETHICAL AND REGULATORY ASPECTS	20
ETHICS COMMITTEE AND REGULATORY APPROVALS	21
INFORMED CONSENT AND PARTICIPANT INFORMATION	21
RECORDS	21
Study Forms	21
Sample Labelling	22
Source documents	22
Direct access to source data / documents	22
DATA PROTECTION	22
QUALITY ASSURANCE & AUDIT.....	23
INSURANCE AND INDEMNITY	23
TRIAL CONDUCT	23
TRIAL DATA	23
RECORD RETENTION AND ARCHIVING	23
DISCONTINUATION OF THE TRIAL BY THE SPONSOR	24
STATEMENT OF CONFIDENTIALITY	24
PUBLICATION AND DISSEMINATION POLICY.....	24
USER AND PUBLIC INVOLVEMENT	24
STUDY FINANCES	24
Funding source	24
Participant stipends and payments	24
SIGNATURE PAGES	26
REFERENCES	27

TRIAL / STUDY BACKGROUND INFORMATION AND RATIONALE

The Centers for Disease Control (CDC) describe vaccinations as among the 10 most significant health achievements ever documented [1]; and for many conditions they have been an unmitigated success (e.g., smallpox) [2]. There are, however, several populations in whom vaccine effectiveness is far from optimal. These populations are typically contending with underlying immune impairment by virtue of their advancing age [3] and/or the presence of co-existing diseases (e.g., cancer). As a consequence, vaccines are most likely to fail those whom they most seek to benefit: individuals at the greatest risk of ill health.

This has prompted research into treatments that enhance immune function prior to vaccination, so called vaccine adjuvants. The aim of such treatments is to optimise the response the immune system makes to the vaccine antigens and, in so doing, increase the likelihood that the vaccine confers protection.

One area in which there has been interest is in the potential for developing psycho-behavioural vaccine adjuvants. There is considerable evidence that psychological and behavioural factors can modulate immunity; with diet [4], physical activity [5], stress [6], affect [7], sleep [8] and social support [9] all associated with immune response.

We recently conducted a longitudinal observational cohort study of multiple psychological (positive affect, negative affect, stress) and behavioural (physical activity, sleep, diet) influences on short and long-term antibody responses to influenza vaccination in older adults. This identified positive affect as the most influential psycho-behavioural factor on influenza-specific antibody responses, independently predicting both short and long-term antibody responses in the weakest immunogenic strain above and beyond known demographic and clinical determinants. For example, correlations between H1N1 antibody response at 16 weeks post-vaccination and positive affect were $r=.30$, with multiple regression models showing positive affect explained 9.1% of additional variation in H1N1 responses beyond age, gender and health status. Intriguingly, we also observed preliminary evidence that positive affect on the day of vaccination was more predictive (14% of variance explained) of antibody responses following vaccination than mood measured over the longer period surrounding vaccination. As influenza-specific antibodies are a well-established correlate of protection from serologically and clinically diagnosed influenza incidence [10], our data suggest that increasing positive affect immediately prior to vaccination could be used as a non-pharmacological vaccine adjuvant.

In order to understand existing approaches to enhancing positive mood, we then conducted a systematic review of existing brief 'mood enhancing' interventions where immune function was also measured. This review identified 31 papers describing 38 single-session interventions that improved mood and where an aspect of immunity was measured (most commonly secretory IgA (SIgA) in 12/ 31 studies). Interventions were varied with the most common being a comedy film or audiotape ($n=15/38$; 39.5%) and music making in the form of group drumming ($n=3$) or singing ($n=4$) were also popular interventions. The remaining interventions included relaxation with or without immune suggestions ($n=3$), mental recall of positive autobiographical events ($n=2$), pleasant or memory retrieving odours ($n=2$), acting out an imagined positive experience ($n=2$), Qi therapy + rest ($n=2$), yoga ($n=1$), Watching film clips of attractive celebrities ($n=1$), Hugging and kissing a romantic partner ($n=1$), and writing about self-congruencies ($n=1$). Despite the variability in intervention approaches, all resulted in an enhancement in positive mood and the vast majority (27/31), in turn, demonstrated a corresponding improvement in immunity. The findings suggest, therefore, that there are multiple effective ways of improving mood in the short-term and that these almost always enhance immunity. However, the majority of these approaches would be

unsuitable for primary care because they can be time consuming, require specialist equipment or space or are labour-intensive. Further, very few studies in our review included older adults as participants. Thus, it remains unclear whether these approaches are appropriate in this population.

To address this - through a series of systematic steps, including focus groups and interviews with older adults and health care professionals, we have recently developed a brief, positive affect intervention – designed to improve short-term mood in older adults and be deliverable within primary care. It is hoped this could act as a psycho-behavioural adjuvant to enhance poor responses to influenza vaccination in older adults. Before performing a definitive trial of the intervention's effectiveness, a feasibility trial is needed for number of reasons:

1. To assess whether our intervention can enhance positive affect (mood)
2. To collect information regarding likely recruitment, effect sizes, and attrition rates for informing the necessary size of a larger definitive trial
3. To examine the practicality and acceptability of delivering the intervention in routine primary care settings
4. To explore the feasibility of obtaining outcome data on healthcare usage for a large scale trial (hospitalisation, GP visits for flu-like symptoms from medical records)

TRIAL / STUDY OBJECTIVES AND PURPOSE

PURPOSE

The purpose of this study is to trial the feasibility of a recently developed positive affect intervention for older adults delivered close to the point of vaccination.

PRIMARY OBJECTIVE

The primary objective of this study is to assess the effects on a positive affect intervention on mood. The effects of the intervention on positive affect will be assessed by change from immediately pre- to post-intervention via self-report using validated instruments including the international short form of positive and negative affect scale [11].

SECONDARY OBJECTIVES

- To collect feasibility measures including recruitment rates, across study attrition, and missing data levels which will be recorded to inform a future definitive trial.
- To obtain effect size estimates for the intervention's influence on non-specific and vaccine specific immunological outcomes.
- To understand the experiences of participants and health care professionals involved in conducting a trial of this nature.

TRIAL / STUDY DESIGN

TRIAL / STUDY CONFIGURATION

Multi-centre, 2 arm parallel randomised controlled feasibility trial. After the trial, a selection of participants and health care professionals involved in the trial will be invited to participate in post-trial focus groups/interviews to inform changes needed for a larger definitive trial.

Primary endpoint

The primary objective of this study is to assess the effects on a positive affect intervention on mood. Therefore, our primary end-point is immediately post-intervention. The primary outcome for analyses will be change in positive affect from pre- to immediately post-intervention as measured by change in validated self-report measures e.g., international short form of the positive and negative affect scale [11].

Secondary endpoint

Recruitment rates, attrition, and missing data levels up to and including 16 weeks post-vaccination.

Secretory IgA concentration change from pre- to immediately post-intervention.

Antibody responses to influenza vaccination at 4 and 16 weeks post-vaccination.

Health service utilisation (e.g., GP visits relating to upper and lower respiratory illnesses, flu-like symptoms, antibiotic prescription, hospitalisation) assessed in medical records at 6 months post-vaccination.

Safety endpoints

We do not expect any safety issues to arise from any aspects of our study.

Stopping rules and discontinuation

Discontinuation of individual participants in the study will occur if a) people indicate a wish to withdraw, or b) if, clinically, there are changes which mean that it would be inappropriate for a person to continue with the study (e.g. illness resulting in severe physical frailty or death which becomes apparent in the time-period between recruitment and study completion).

RANDOMIZATION AND BLINDING

Participants will be individually randomised on a 1:1 ratio to either the experimental or active control arm. The randomisation either be implemented by a software algorithm on a package (e.g., OpenSesame software or similar) that will be used to present questionnaires and the intervention/control video on a computer tablet device to participants or independently by a third party using an online randomization service (www.randomization.com). Randomisation will be implemented such that researchers are unaware of participant assignment.

Participants will not be informed about the nature of each assignment and will be given the same instructions regardless of condition. In this regard, the participants will be blind the nature of the other condition.

All researchers will be blinded to the participant assignment until the end of the study.

For involvement in post-trial focus groups/interviews, participants ID numbers will be entered into an excel database and will be randomly selected to take part using the RANDOM() function.

Maintenance of randomisation codes and procedures for breaking code

Allocations will only be identified at the end of the study. We foresee no scenarios in which allocations would need to be revealed at an earlier point on safety grounds.

TRIAL/STUDY MANAGEMENT

The Chief investigator and other members of the study team (e.g., site principle investigators) will be responsible for obtaining informed consent, data collection and analysis. The analysis will be performed by the Chief investigator with oversight from the Study Statistician.

The Chief Investigator has overall responsibility for the study and shall oversee all study management.

The data custodian will be the Chief Investigator.

DURATION OF THE TRIAL / STUDY AND PARTICIPANT INVOLVEMENT

Study Duration: Enrolment will begin in August 2017 and cease when sufficient participants have been recruited or January 2018 (whichever is earliest). The active part of the trial will end when the final participant attends their 16 week post-vaccination follow-up (anticipated March/April 2018). Although post-trial focus groups and examination of medical records will occur at up to 6 months post-vaccination.

Participant Duration: 16 Weeks. Intervention will occur at baseline, prior to receipt of vaccination. Follow-up visits will occur at 4 weeks and 16 weeks post-vaccination. Medical records will be accessed at 6 months post-vaccination to examine health service utilization.

End of the Trial

The end of the active portion of the study will be the last visit of the last participant, 16 weeks post-vaccination. However, medical records will be examined at 6 months post-vaccination for all participants to examine health service utilization.

SELECTION AND WITHDRAWAL OF PARTICIPANTS

Recruitment

Approximately 110 adults aged 65-85 years, who would normally be invited to receive the seasonal influenza vaccine as part of usual care, will be recruited from primary care. According to recent NHS information centre data, a typical medium sized practice has between 4000 to 7999 patients. Approximately 14% of these will be aged between 65-85 years. A typical medium sized practice could, therefore, identify between 560 and 1120 eligible patients; and a sample size of 110 would require 10-20% of eligible patients to participate. Thus, we will seek to recruit from 2 practices (to be identified with assistance of

clinical research network) to maximise the probability of meeting this recruitment target. If early recruitment levels are below expectation, a third practice may be used as an additional study site.

Participants will be recruited from primary care clinics. The initial approach will be via invitation letter from the patient's GP, and information about the study will be provided.

The investigator or their nominee, e.g. from the research team or a member of the participant's usual care team, will inform the participant, of all aspects pertaining to participation in the study if the patient expresses interest by returning a reply slip.

It will be explained to the potential participant that entry into the trial is entirely voluntary and that their treatment and care will not be affected by their decision. It will also be explained that they can withdraw at any time. If the participant wishes to withdraw then they can request the erasure of any collected, but not yet analysed, data by contacting the chief investigator. Should the participant lose capacity to consent during the study they will be withdrawn from the study. Identifiable data or samples already collected with consent would be retained and used in the study. No further data or samples would be collected or any other research procedures carried out in relation to that participant.

Eligibility criteria

For Feasibility Trial:

Inclusion criteria

Males and Females aged 65-85 years (inclusive)
Received influenza vaccination for the 2016/17 season
Eligible to receive 2017/18 influenza vaccination as part of usual care
Ability to give informed consent

Exclusion criteria

Males and Females aged less than 65 or over 85 years (exclusive)
Did not receive influenza vaccination for the 2016/17 season
Ineligible to receive 2017/18 influenza vaccination as part of usual care
Unable to provide informed consent
Deemed by health care provider to be:
Too physically frail to participate
Diagnosed with dementia or other cognitive condition which would make participation difficult
Insufficient command of English language
Influenza vaccination contraindicated
Sufficiently impaired of hearing or vision that exposure to the intervention or control video content as intended would be compromised
Those for whom the collection of blood samples is contraindicated.

For Post-Trial Staff Interviews:

Inclusion criteria

Member of staff at a GP practice site involved in the feasibility trial
Aware of and observed aspects of the feasibility trial at their site

Exclusion criteria

Not staff at a GP practice site involved in the feasibility trial
Unaware of or did not observe any aspect of the feasibility trial at their site

Expected duration of participant participation

Study participants will be participating in the study for 16 weeks. Although participants medical records will be accessed at 6 months post-vaccination to examine health care utilization.

Removal of participants from therapy or assessments/Participant Withdrawal

Participants may be withdrawn from the trial either at their own request or at the discretion of the Investigator or on the advice of their health care professional (for example on the basis of health or inability to continue). The participants will be made aware that this will not affect their future care. Participants will be made aware (via the information sheet and consent form) that should they withdraw the data collected to date cannot be erased and may still be used in the final analysis. Participant who withdraw after randomisation will not be replaced.

Informed consent

All participants will provide written informed consent. The Informed Consent Form will be signed and dated by the participant before they enter the trial. The Investigator will explain the details of the trial and provide a Participant Information Sheet, ensuring that the participant has sufficient time to consider participating or not. The Investigator will answer any questions that the participant has concerning study participation.

Informed consent will be collected from each participant before they undergo any interventions related to the study. One copy of this will be kept by the participant, one will be kept by the Investigator, and a third will be retained in the patient's medical records.

Should there be any subsequent amendment to the final protocol, which might affect a participant's participation in the trial, continuing consent will be obtained using an amended Consent form which will be signed by the participant.

TRIAL / STUDY TREATMENT AND REGIMEN

Study participants will:

Be identified as meeting inclusion or exclusion criteria by their GP practice. Those eligible for participation will receive a letter from their GP, detailing the nature of the study, and inviting them take part. Those wishing to take part will return a reply slip, in a freepost envelope provided, to researchers.

Researchers will contact participants who indicated they wanted to take part to arrange a time to discuss the research. Participants will be provided with an information sheet, have the opportunity to ask any questions they may have regarding the study and will provide informed consent if they are happy to participate. Participants expressing interest in the study and

giving consent will receive and be asked to complete a short questionnaire containing questions to ascertain the following demographic details:

- Age
- Gender
- Ethnicity
- Education
- Household income
- Occupation
- Marital status
- Living status
- Smoking status

A trait version of the positive and negative affect scale [12] and the emotional reactivity scale [14], the Health Status Questionnaire [16] and the Life Orientation Test – Revised [17], which is a measure of dispositional optimism. Participants will be asked to return this questionnaire in a freepost envelope or at their first GP study visit.

First Visit to GP Surgery

Participants will be randomised into one of two trial conditions (Experimental, Active Control).

In both conditions, participants will have a pre-vaccination blood sample (approx. 8ml) taken via venepuncture (necessary for post-vaccine comparisons). Following this, participants will be asked to provide a saliva sample using the passive drool method technique before and after vaccination, and complete pre-intervention questionnaires to assess current mood. These will include the Positive and Negative Affect Scale [12], Two Visual Analogue items [13], and a single item mood measure developed for the present study using pictures (including older adult faces) to help represent mood states.

Participants will then individually view a 15-20 minute video package on a tablet or similar audio/visual device. The content of the video will differ according to their random assignment.

Experimental Condition

Participants in the experimental condition will view a video designed to induce positive affect. This includes 3 short comedy clips (fork handles sketch, the two Ronnie's; A room with a view – faulty towers; Tim Vine Live stand-up extract), uplifting music (Jailhouse Rock - Elvis Presley; Happy Together – The Turtles), jokes and positive imagery. The content of the intervention has been informed by patient and public involvement, focus groups with older adults, and pilot testing.

The full video can be viewed at: <https://youtu.be/U7QNfKOa19I>

Control Condition

Participants in the control condition will view a video of matched length to the experimental condition video, but not designed to induce mood change. This includes short documentary clips (a pride in pencils; model railways, lecture extract on hydration), neutral music and images.

The full video can be viewed at: <https://youtu.be/h5X5mmydbEU>

After viewing their respective videos, participants will provide a second saliva sample and repeat the same mood assessment questionnaires as listed above. Participants will then receive a standard dose of the 2017/18 influenza vaccination (as part of usual care).

Second Visit to GP Surgery (4 weeks post-vaccination)

Four weeks after the first visit, participants will be asked to return to their GP surgery, where they will have a follow-up blood sample taken (approx. 8ml) via venepuncture.

Third Visit to GP Surgery (16 Weeks Post-vaccination)

16 weeks after the first visit, participants will be asked to return to their GP surgery, where they will have a follow-up blood sample taken (approx. 8ml) via venepuncture.

Post-Trial Qualitative Interviews

At the completion of the third visit to the GP surgery, a random selection of 20 participants will be invited to participate in post-trial focus groups or interviews, that will last approximately 1 hour, regarding the study and intervention design. Topics that will be addressed in the focus group include: the acceptability of the intervention, what worked and what didn't work for them and whether they felt it was suitable for wider use (or if not how it should be changed).

Separately a focus group or individual interviews (depending on availability) will be run with 3-4 HCPs from the study site(s), however, greater emphasis will be placed on the practicality of intervention delivery, and barriers and facilitators to delivery.

Focus groups/interviews will be recorded and analysed for common themes using thematic analysis in a constant comparative approach [15].

Compliance

Compliance is defined as the proportion of participants that complete baseline assessments, observe the intervention/control video; receive influenza vaccination and attend at least one post-vaccination visit for blood sampling.

Criteria for terminating trial

We do not anticipate the study will be terminated early.

TRANSPORT AND STORAGE OF THE TISSUES

Samples will be stored in linked anonymised format at the place of collection and labelled using a combination of date of birth, initials and study number to permit accurate linkage to clinical data and the consent form.

The master database will be held by the co-ordinating centre in a password encrypted file.

Blood samples will be collected in gold-topped vacutainers (approximately 8ml). Serum will be isolated, aliquoted and stored at -80 degrees centigrade. The analysis of serum samples will take place at the University of Nottingham within the School of Life Sciences, and also at other authorised laboratories within the University of Nottingham.

Page 18 of 27

Mood and Influenza Vaccine Response: A Feasibility Trial Protocol Final 1.1 21/08/17

<p>This protocol is confidential and the property of the University of Nottingham. No part of it may be transmitted, reproduced, published, or used by others persons without prior written authorisation from the University of Nottingham</p>

Saliva samples (approximately 2ml) will be collected in polypropylene tubes. Saliva will be frozen and stored at -20 degrees centigrade. The analysis of serum samples will take place at the University of Northumbria, and also at other authorised laboratories within the University of Northumbria.

Samples will be collected and transferred from the place of collection to the respective collaborators in batch shipments by courier as frequently as required. All shipments will contain a complete inventory of all samples, along with the name of the person responsible for sending the samples. If participants are agreeable and sign the optional clause on the consent form, once analysis has taken place, samples will be placed into storage at the University of Nottingham. Where participants do not agree to the future use of the samples they will be destroyed in accordance with the Human Tissue Act, 2004.

LABORATORY ANALYSES

Laboratory analyses will be conducted on blood and saliva samples taken from participants.

Blood Samples

Blood Samples will be assessed for a variety of immunological parameters relevant to vaccine response (e.g., IgG and hemagglutination inhibiting antibody levels). They may also be analysed for other immunological parameters relevant to the immune and endocrine response to vaccination and/or mood induction (e.g., cytokines). The analyses will be conducted by the Chief Investigator, overseen by co-investigators Lucy Fairclough, Paddy Tighe and Ian Todd. All analyses will be completed at the University of Nottingham using equipment and laboratories serviced and managed at the University of Nottingham.

Saliva Samples

Saliva Samples will be primarily assessed for secretory IgA. They may also be analysed for other immunological parameters relevant to the immune and endocrine response to vaccination and/or mood induction (e.g., cortisol). The analyses will be conducted by laboratory technicians at the University of Northumbria, overseen by co-investigator Mark Wetherell. All analyses will be completed at the University of Northumbria using equipment and laboratories serviced and managed at the University of Northumbria.

STATISTICS

Methods

Analyses will be primarily performed by Kieran Ayling, with input from the project statistician (Graziella Figueredo) using SPSS and Stata software packages.

While many outcomes of interest will be descriptive in nature (e.g., attrition, recruitment rates), between study arm comparisons will be made on a number of primary and secondary outcomes (positive affect, antibody response, S-IgA concentration, flu-like symptoms, health service utilization) using appropriate statistical tests (e.g., t-tests, ANOVA). Intention-to-treat analyses will be favoured where appropriate.

Sample size and justification

As a feasibility study, the sample size has been selected to inform the design of a future definitive RCT allowing us to examine recruitment uptake levels, attrition, intervention engagement, and suitability of data collection methods. It is not our aim to be powered to detect effects in vaccine specific outcomes (e.g., antibody responses, rates of flu like illness) but to provide initial effect size estimates for a future larger RCT. However, our sample size will be sufficient to provide adequate power to detect between pre-post differences in positive affect between the intervention and active control arms. Our power calculation (two-tailed dependent t-test difference in means) is based on the intervention demonstrating a medium effect size ($d_z = .5$) on mood. A sample of 45 participants would be needed per arm to provide 95% power to detect pre-post differences. We will, therefore, aim to recruit 55 participants per intervention arm to allow for attrition.

Assessment of efficacy

Efficacy of the intervention will be assessed by a significantly larger change in at least one of our positive affect measures (e.g., pre-post differences in PANAS scores) in the experimental condition than in the control condition.

Secondary efficacy assessments will be made in relation to secretory IgA levels and vaccination responses however this will be to provide an effect size estimate for a future definitive trial – rather than an efficacy endpoint per se.

Assessment of safety

We do not expect any safety issues to arise from any aspects of our study and therefore have no safety endpoint per se.

Procedures for missing, unused and spurious data

Missing and spurious data will be recorded to assess relevance and usefulness of measures. Where deemed appropriate by the study statistician, some data may be imputed from previous participant or mean observations.

Definition of populations analysed

Analysis will be conducted of a full data set for all participants who are deemed to have no major protocol violations that could interfere with the objectives of the study. Such a set will comprise all participants, who complete baseline assessment (and consent form) and for whom post-baseline assessment of the primary outcome measure is available.

ADVERSE EVENTS

The occurrence of an adverse event as a result of participation is not expected. However, participants may experience some bruising and minor discomfort or feeling faint following blood sampling (usual side-effects of venepuncture). These will not be considered an adverse event.

ETHICAL AND REGULATORY ASPECTS

ETHICS COMMITTEE AND REGULATORY APPROVALS

The trial will not be initiated before the protocol, informed consent forms and participant and GP information sheets have received approval / favourable opinion from the Research Ethics Committee (REC), the respective National Health Service (NHS) or other healthcare provider's Research & Development (R&D) department, and the Health Research Authority (HRA) if required. Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed consent forms and participant information sheets (if appropriate) have been reviewed and received approval / favourable opinion from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of Good Clinical Practice, and the Department of Health Research Governance Framework for Health and Social care, 2005.

INFORMED CONSENT AND PARTICIPANT INFORMATION

The process for obtaining participant informed consent will be in accordance with the REC guidance, and Good Clinical Practice (GCP) and any other regulatory requirements that might be introduced. The investigator or their nominee and the participant shall both sign and date the Informed Consent Form before the person can participate in the study.

The participant will receive a copy of the signed and dated forms and the original will be retained in the Trial Master File. A second copy will be filed in the participant's medical notes and a signed and dated note made in the notes that informed consent was obtained for the trial.

The decision regarding participation in the study is entirely voluntary. The investigator or their nominee shall emphasize to them that consent regarding study participation may be withdrawn at any time without penalty or affecting the quality or quantity of their future medical care, or loss of benefits to which the participant is otherwise entitled. No trial-specific interventions will be done before informed consent has been obtained.

The investigator will inform the participant of any relevant information that becomes available during the course of the study, and will discuss with them, whether they wish to continue with the study. If applicable they will be asked to sign revised consent forms.

If the Informed Consent Form is amended during the study, the investigator shall follow all applicable regulatory requirements pertaining to approval of the amended Informed Consent Form by the REC and use of the amended form (including for ongoing participants).

RECORDS

Study Forms

Each participant will be assigned a trial identity code number, allocated at randomisation if appropriate, for use on study forms other trial documents and the electronic database. This

identity code will also use a jumbled combination of their initials (of first and last names) and date of birth (dd/mm/yy).

Study forms will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Participant Trial Number (the Trial Recruitment Log), to permit identification of all participants enrolled in the trial, in accordance with regulatory requirements and for follow-up as required. Study forms shall be restricted to those personnel approved by the Chief or local Principal Investigator and recorded on the 'Trial Delegation Log.'

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.

The Chief or local Principal Investigator shall sign a declaration ensuring accuracy of data recorded in the study forms.

Sample Labelling

Each participant will be assigned a trial identity code number for use on the samples, consent forms and other study documents and the electronic database. This identity code will also use a jumbled combination of their initials (of first and last names) and date of birth (dd/mm/yy).

Source documents

Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and records. A study form may also completely serve as its own source data. Only trial staff as listed on the Delegation Log shall have access to trial documentation other than the regulatory requirements listed below.

Direct access to source data / documents

The study forms and all source documents, including progress notes and copies of laboratory and medical test results shall made be available at all times for review by the Chief Investigator, Sponsor's designee and inspection by relevant regulatory authorities (e.g. DH, Human Tissue Authority).

DATA PROTECTION

All trial staff and investigators will endeavour to protect the rights of the trial's participants to privacy and informed consent, and will adhere to the Data Protection Act, 1998. The study forms will only collect the minimum required information for the purposes of the trial. Study forms will be held securely, in a locked room, or locked cupboard or cabinet. Access to the information will be limited to the trial staff and investigators and relevant regulatory authorities (see above). Computer held data including the trial database will be held securely and password protected. All data will be stored on a secure dedicated web server. Access will be restricted by user identifiers and passwords (encrypted using a one way encryption method). Information about the trial in the participant's medical records / hospital notes will be treated confidentially in the same way as all other confidential medical information.

Electronic data will be backed up every 24 hours to both local and remote media in encrypted format.

QUALITY ASSURANCE & AUDIT

INSURANCE AND INDEMNITY

Insurance and indemnity for trial participants and trial staff is covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under cover of HSG (96)48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaints procedures.

The University of Nottingham as research Sponsor indemnifies its staff, research participants and research protocols with both public liability insurance and clinical trials insurance. These policies include provision for indemnity in the event of a successful litigious claim for proven non-negligent harm.

TRIAL CONDUCT

Trial conduct may be subject to systems audit of the Trial Master File for inclusion of essential documents; permissions to conduct the trial; Trial Delegation Log; CVs of trial staff and training received; local document control procedures; consent procedures and recruitment logs; adherence to procedures defined in the protocol (e.g. inclusion / exclusion criteria, correct randomisation, timeliness of visits); adverse event recording and reporting; accountability of trial materials and equipment calibration logs.

TRIAL DATA

Monitoring of trial data shall include confirmation of informed consent; source data verification; data storage and data transfer procedures; local quality control checks and procedures, back-up and disaster recovery of any local databases and validation of data manipulation. The Trial Coordinator/ or where required, a nominated designee of the Sponsor, shall carry out monitoring of trial data as an ongoing activity.

Entries on study forms will be verified by inspection against the source data. A sample of study forms (10% or as per the study risk assessment) will be checked on a regular basis for verification of all entries made. In addition the subsequent capture of the data on the trial database will be checked. Where corrections are required these will carry a full audit trail and justification.

Trial data and evidence of monitoring and systems audits will be made available for inspection by REC as required.

RECORD RETENTION AND ARCHIVING

In compliance with the ICH/GCP guidelines, regulations and in accordance with the University of Nottingham Research Code of Conduct and Research Ethics, the Chief or local Principal Investigator will maintain all records and documents regarding the conduct of the study. These will be retained for at least 7 years or for longer if required. If the responsible investigator is no

longer able to maintain the study records, a second person will be nominated to take over this responsibility.

The Trial Master File and trial documents held by the Chief Investigator on behalf of the Sponsor shall be finally archived at secure archive facilities at the University of Nottingham. This archive shall include all trial databases and associated meta-data encryption codes.

DISCONTINUATION OF THE TRIAL BY THE SPONSOR

The Sponsor reserves the right to discontinue this trial at any time for failure to meet expected enrolment goals, for safety or any other administrative reasons. The Sponsor shall take advice from the Trial Steering Committee and Data Monitoring Committee as appropriate in making this decision.

STATEMENT OF CONFIDENTIALITY

Individual participant medical information obtained as a result of this study are considered confidential and disclosure to third parties is prohibited with the exceptions noted above. Participant confidentiality will be further ensured by utilising identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

If information is disclosed during the study that could pose a risk of harm to the participant or others, the researcher will discuss this with the CI and where appropriate report accordingly.

Data generated as a result of this trial will be available for inspection on request by the participating physicians, the University of Nottingham representatives, the REC, local R&D Departments and the regulatory authorities.

PUBLICATION AND DISSEMINATION POLICY

Results from this study will be written up for publication in leading academic journals in the field (e.g., Brain, Behaviour and Immunity) in the year following study completion. No participants will be identified in these publications.

USER AND PUBLIC INVOLVEMENT

This study has benefited from input from patient and public involvement (Adults aged 65-85) whose input was sought for the purpose of the proposed study, including intervention content and participant documentation. We would like to thank those who participated for their advice and input.

STUDY FINANCES

Funding source

This research is funded by the National Institute for Health Research - School for Primary Care Research (NIHR SPCR)

Participant stipends and payments

Participants will receive up to £20 (£10 per non-standard visit to GP surgery) in inconvenience payments for participation in the study, travel and parking costs. Additionally, those participants who take part in the post-trial focus groups will receive a further £20 inconvenience payment.

SIGNATURE PAGES

Signatories to Protocol:

Chief Investigator: (name)_____Kieran Ayling_____

Signature:_____

Date: _____

Co- investigator: (name)_____Kavita Vedhara_____

Signature:_____

Date: _____

Trial Statistician: (name)_____Grazziela Figueredo_____

Signature:_____

Date: _____

REFERENCES

- 1 Global Public Health Achievements Team CDC. Ten Great Public Health Achievements-Worldwide, 2001-2010 (Reprinted from MMWR vol 60, pg 814-818, 2011). *JAMA* 2011;**306**:484–7.
- 2 Andre F, Booy R, Bock H, *et al.* Vaccination greatly reduces disease, disability, death and inequity worldwide. *Bull World Health Organ* 2008;**86**:140–6.
- 3 Jefferson T, Rivetti D, Rivetti a., *et al.* Efficacy and effectiveness of influenza vaccines in elderly people: A systematic review. *Lancet* 2005;**366**:1165–74. doi:10.1016/S0140-6736(05)67339-4
- 4 Calder PC, Jackson A. Undernutrition, infection and immune function. *Nutr Res Rev* 2000;**13**:3–29. doi:10.1079/095442200108728981
- 5 Simpson R, Spielmann G. Exercise and Immunosenescence. In: Bosch J, Phillips A, Lord J, eds. *Immunosenescence*. New York: : Springer Science 2013. 159–78.
- 6 Segerstrom S, Miller G. Psychological Stress and the Human Immune System: A Meta-Analytic Study of 30 Years of Inquiry. *Psychol Bull* 2004;**130**:601–30. doi:10.1037/0033-2909.130.4.601
- 7 Pressman S, Cohen S. Does Positive Affect Influence Health? *Psychol Bull* 2005;**131**:925–71. doi:10.1037/0033-2909.131.6.925
- 8 Bryant P, Trinder J, Curtis N. Sick and tired: Does sleep have a vital role in the immune system? *Nat Rev Immunol* 2004;**4**:457–67. doi:10.1038/nri1369
- 9 Uchino B. Social Support and Health: A Review of Physiological Processes Potentially Underlying Links to Disease Outcomes. *J Behav Med* 2006;**29**:377–87. doi:10.1007/s10865-006-9056-5
- 10 Coudeville L, Bailleux F, Riche B, *et al.* Relationship between haemagglutination-inhibiting antibody titres and clinical protection against influenza: development and application of a bayesian random-effects model. *BMC Med Res Methodol* 2010;**10**:18. doi:10.1186/1471-2288-10-18
- 11 Thompson E. Development and Validation of an Internationally Reliable Short-Form of the Positive and Negative Affect Schedule (PANAS). *J Cross Cult Psychol* 2007;**38**:227–42. doi:10.1177/0022022106297301
- 12 Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. *J Pers Soc Psychol* 1988;**54**:1063–70. doi:10.1037/0022-3514.54.6.1063
- 13 Betella A, Verschure PF. The affective slider: a digital self-assessment scale for the measurement of human emotions. *PloS one*. 2016 Feb 5;11(2):e0148037.
- 14 Nock MK, Wedig MM, Holmberg EB, *et al.* The Emotion Reactivity Scale: Development, Evaluation, and Relation to Self-Injurious Thoughts and Behaviors. *Behav Ther* 2008;**39**:107–16. doi:10.1016/j.beth.2007.05.005
- 15 Glaser B. The Constant Comparative Method of Qualitative Analysis. *Soc Probl* 1965;**12**:436–45.
- 16 Radosevich D, Pruitt M. Twelve-item health status questionnaire: HSQ-12 version 2.0. Health Outcomes Institute. 1995.
- 17 Scheier MF, Carver CS, Bridges MW. Distinguishing optimism from neuroticism (and trait anxiety, self-mastery, and self-esteem): a reevaluation of the Life Orientation Test. *Journal of personality and social psychology*. 1994 Dec;67(6):1063.